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Antimicrobial Activity of 8-Hydroxyquinoline and Transition Metal Complexes

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Abstract: Heterocyclic compounds like 8-hydroxyquinoline (8HQ) and derivatives have been found in natural products and therapeutics. Herein 8HQ and metal complexes of 8HQ-5-substituted (X) uracils, X = I, NO_2 (1-6) were investigated for their antimicrobial potency. The complexes 1-6 exhibited growth inhibition against many strains of gram-positive and gram-negative bacteria with minimum inhibitory concentrations (MICs) of 575.71-718.76 μM. The investigated compound 8HQ was shown to be a very strong antimicrobial agent with the MIC of 27.58 μM that comparable to ampicillin (MIC 26.93 μM), the reference drug. The activity of 8HQ mostly was observed for resistant pathogens, gram- positive bacteria e.g. *Staphylococcus aureus*, *Enterococcus faecalis* and diploid fungus, *Candida albicans*. The findings reveal 8HQ as the very potent antimicrobial agent and a series of 8HQ transition metal complexes as novel antimicrobials as well as the applications of 8HQ for the design and synthesis of new and potential therapeutic lead compounds.

Key words: Antimicrobial activity, 8-hydroxyquinoline, uracils, metal complex

INTRODUCTION

Heterocyclic compounds such as 8-hydroxyquinoline (8HQ), is originated from root of *Sebastiana corniculata* (Jeon *et al*., 2009). Its derivatives have been found in many natural products e.g. 4-formyl-8-hydroxyquinoline from *Broussonetia zeylanica* (Ileperuma *et al*., 1989) and in therapeutics as antibacterials (Tanzer *et al*., 1978), antifungals (Anjaneyulu *et al*., 1982; Jeon *et al*., 2009) as well as used for treatment of tuberculosis, diabetes and malaria (Dixit *et al*., 2011). Derivatives of 8HQ have been used as topical antiseptics and internal disinfectants that apparently exhibit low toxicity for humans (Tanzer *et al*., 1978). To date, microbial infection is one of the major problem worldwide, due to the increasing rate of resistance. Resistant pathogens have been found among both gram-positive and gram-negative bacteria. However, the high natural resistance to antimicrobials is frequently observed in many gram-positive bacteria. These organisms, e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin resistant enterrococci (VRE) are capable of rapidly becoming resistant to many commonly used antimicrobial drugs and are causative agents of nosocomial and community acquired infections (Lawung *et al*., 2010). Particularly, *S. aureus* is the most common cause of bacterial nosocomial infection (Diekema *et al*., 2001) such as in patient with severe burns (Mayhall, 2003; Ressner *et al*., 2008). In addition, *Klebsiella pneumoniae* is the gram-negative bacteria causing nosocomial infection and becoming a major problem in many hospitals (Garcia-Fernandaz *et al*., 2012). The enhanced bioactivities of some drugs (oxaprofin, aspirin and ibuprofen) (Dutta *et al*., 2004) or natural compounds e.g. flavonoids and phenolics (Kostyuk *et al*., 2004; Mahal *et al*., 2005) when prepared as their metal complexes are well recognized (Ileperuma *et al*., 1989; Shen *et al*., 1999; Galal *et al*., 2010; Liu *et al*., 2010). So far a number of bioactive metal complex based compounds

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such as anticancers, antioxidants and antimicrobials have been documented (Suksrichavalit *et al*., 2008 and 2009; Colak *et al*., 2010; Galal *et al*., 2010; Liu *et al*., 2010). Recently, mixed ligand metal complexes of uracils and 8HQ have been reported (Prachayasittikul *et al*., 2012). These metal complexes displayed significant cytotoxicity against human cancer cell lines including human hepatocellular carcinoma (HepG2), human lung carcinoma (A549), human cholangiocarcinoma (HuCCA-1) and T-lymphoblast (MOLT-3, acute lymphoblastic leukemia) cells as well as antioxidant properties (Prachayasittikul *et al*., 2012). In the previous studies, it was found that copper-pyridine derivatives complexes with antioxidant activity, also displayed antimicrobial activity (Suksrichavalit *et al*., 2008 and 2009). To search for new antimicrobials with potential to combat resistant pathogens, therefore, mixed ligand (8HQ-uracils) transition metal complexes were explored. The uracils in this study were 5-iodouracil (5Iu) and 5-nitrouracil (5Nu). The title 8HQ and 8HQ-uracils metal complexes were investigated for their antimicrobial potency.

MATERIALS AND METHODS

Test compounds: Transition metal complexes of 8HQ-5Iu 1-3 (Fig. 1a) and 8HQ-5Nu 4-6 (Fig. 1b) were prepared and confirmed by spectral data (Prachayasittikul *et al*., 2012). The ligands 8HQ, 5Iu and 5Nu were shown in Fig. 1c.

Antimicrobial testing: Antimicrobial activity of the tested compounds was performed using the agar dilution method as previously described (Prachayasittikul *et al*., 2011). The tested compounds dissolved in DMSO were individually mixed with 1 mL Mueller Hinton (MH) broth. The solution was then transferred to the MH agar solution to give the final concentrations of 256-2 μg mL^{-1}. The MH broth was used as a negative control. Microorganisms were cultured in MH broth at 37°C for 24 h and diluted with 0.9% normal saline solution to adjust the cell density of 1×10^{8} cell mL^{-1}. The microorganisms were inoculated onto each plate and further incubated at 37°C for 24-48 h. Cell growth inhibition of the compounds were determined. Twenty-seven tested microorganisms were gram-negative bacteria: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Serratia macescens* ATCC 8100, *Salmonella typhimurium* ATCC 13311, *Shewanella putrefaciens* ATCC 8071, *Achromobacter xylosoxidans* ATCC 2706, *Pseudomonas aeruginosa* ATCC 15442, *Pseudomonas stutzeri* ATCC 17587, *Shigella dysenteriae*, *Salmonella enteritidis*, *Morganella morganii*, *Aeromonas hydrophila*, *Citrobacter freundii*, *Plesiomonas shigelloides*; gram-positive bacteria: *Staphylococcus aureus* ATCC 29213, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Enterococcus faecalis* ATCC 29212, *Enterococcus faecalis* ATCC 33186, *Micrococcus luteus* ATCC 10240, *Corynebacterium diphtheriae* NCTC 10356, *Bacillus subtilis* ATCC 6633, *Streptococcus pyogenes*, *Listeria monocytogenes*, *Bacillus cereus* and diploid fungus (yeast): *Candida albicans* ATCC 90028, *Saccharomyces cerevisiae* ATCC 2601.

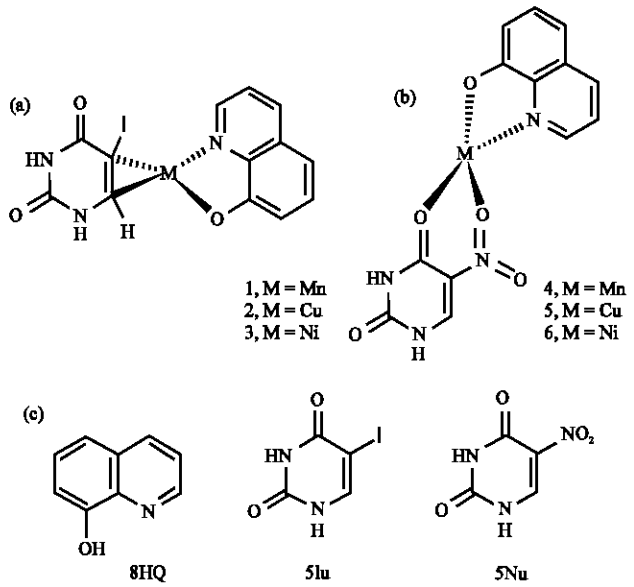

Fig. 1(a-c): (a) Structures of 8HQ-5Iu metal complexes 1-3, (b) 8HQ-5Nu metal complexes 4-6 and (c) Ligands 8HQ, 5 Iu and 5 Nu

RESULTS AND DISCUSSION

The synthesized 8HQ transition metal (Mn, Cu, Ni) complexes 1-6 were tested in parallel with the free ligands (8HQ, 5Iu and 5Nu) and vehicle (DMSO) using the agar dilution method (Prachayasittikul *et al*., 2011) against twenty-seven strains of microorganisms. The results (Table 1) showed that all compounds inhibited the growth of both gram-positive and gram-negative bacteria. The DMSO was tested in parallel with the compounds, but showed no effect toward the tested microorganisms. The complexes 1 (Mn), 2 (Cu) and 5 (Cu) exhibited antigrowth activity against *S. pyogenes*, *S. dysenteriae, P. shigelloides* and *B. cereus* with minimum inhibitory concentrations (MICs) of 578.08, 575.71 and 701.80 μM, respectively. Nickel complexes 3 and 6 exerted antibacterial activity against *S. pyogenes* and *P. shigelloides* with the MICs of 582.06 and 711.25 μM, respectively. Manganese complex 4 showed the inhibition against *S. pyogenes*, *S. dysenteriae* and *A. hydrophila* (MIC 718.76 μM). In addition, the Cu complex 5 displayed antibacterial activity against *S. typhimurium* ATCC 13311, *S. putrefaciens* ATCC 8071, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *E. faecalis* ATCC 33186, *C. diphtheriae* NCTC 10356 and *A. hydrophila* with the MIC of 701.80 μM. Interestingly, all of the tested 8QH metal complexes 1-6 exerted their activities against the *S. pyogenes*. The free ligands; 5 Iu and 5 Nu were shown to be inactive antimicrobials. Whereas the 8HQ ligand inhibited the growth of tested microorganisms, particularly, the resistant pathogen such as *S. aureus* including fungus, *C. albicans* and *S. cerevisiae* with the MIC of 27.58 μM that comparable to the MIC (26.93 μM) of ampicillin, the reference drug. Relatively strong antibacterial action of 8HQ was observed against *M. luteus* ATCC 10240 with MIC of 55.15 μM and *A. hydrophila* (MIC 110.30 μM). The organisms that were inhibited by 8HQ (MIC 220.61 μM) including *E. coli* ATCC 25922, *S. macescens* ATCC 8100, *S. typhimurium* ATCC 13311, *P. stutzeri* ATCC 17587, *S. putrefaciens* ATCC 8071, *A. xylosoxidans* ATCC 2706, *S. enteritidis* and *C. freundii*. In addition, 8HQ showed antigrowth activity against *K. pneumoniae* ATCC 700603 and *M. morganii* with MIC value of 441.22 μM. The antibacterial activity of 8HQ against *P. aeruginosa* ATCC 15442 was noted at high MIC value (1764.87 μM). The results indicated that the 8HQ when formed metal (Mn, Cu, Ni) complexes with 5Iu or 5Nu provided the compounds with lower antimicrobial activity. This could be resulted from a higher ability of N,O atoms electron donors of the free ligand, 8HQ that chelated metal ions leading to [metal-(8HQ)x-(H_2O)y] complexes that are essential for the inhibition of bacteria (Hadda *et al*., 2009). On the other hand, the ligand chelating effect in the living cells protects the growth of microorganisms. However, the antimicrobial activity of these Mn, Cu, Ni complexes 1-6 was not reported in the literature. Previously, a series of mixed ligand Hg (II) complexes (8HQ-Hg-Salicylic acids) was reported to be antibacterials and antifungals with either equal or slightly higher activity than the bis-chelate

Table 1: Antimicrobial activity of metal complexes 1-6 and 8-hydroxyquinoline

Compound[a,b]	Microorganism	MIC[c] (μM)
8HQ-Mn-5Iu	*S. pyogenes, S. dysenteriae, P. shigelloides, B. cereus, E. faecalis* ATCC 29212	587.08
8HQ-Cu-5Iu	*S. pyogenes, S. dysenteriae, P. shigelloides, B. cereus*	575.71
8HQ-Ni-5Iu	*S. pyogenes, P. shigelloides, B. cereus*	582.06
8HQ-Mn-5Nu	*S. pyogenes, S. dysenteriae, A. hydrophila*	718.76
8HQ-Cu-5Nu	*S. pyogenes, S. dysenteriae, P. shigelloides, B. cereus, S. typhimurium* ATCC 13311, *S. putrefacieus* ATCC 8071, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *E. faecalis* ATCC 33186, *C. diphtheriae* NCTC 10356, *A. hydrophila*	701.80
8HQ-Ni-5Nu	*S. pyogenes, P. shigelloides*	711.25
8HQ	*S. pyogenes, S. dysenteriae, P. shigelloides, B. cereus, S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *E. faecalis* ATCC 29212, *E. faecalis* ATCC 33186, *B. subtilis* ATCC 6633, *C. diphtheriae* NCTC 10356, *L. monocytogenes*, *S. cerevisiae* ATCC 2601, *C. albicans* ATCC 90028	27.58
	M luteus ATCC 10240	55.15
	A. hydrophila	110.30
	E. coli ATCC 25922, *S. macesceus* ATCC 8100, S. *typhimurium* ATCC 13311, *P. stutzeri* ATCC 17587, *S. putrefacieus* ATCC 8071, *A. xylosoxidans* ATCC 2706, *S. enteritidis*, *C. freundii*	220.61
	K. pneumoniae ATCC 700603, *M. morganii*	441.22
	P. aeruginosa ATCC 15442	1764.87

[a]Ampicillin at 26.93 μM was used as a control of antimicrobial testing system, it showed complete inhibition against *S. typhimurium* ATCC 13311, *P. stutzeri* ATCC 17587, *C. diphtheriae* NCTC 10356, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *M. luteus* ATCC 10240, *B. subtilis* ATCC 6633, *S. pyogenes*, *L. monocytogenes* and *P. shigelloides*, [b]Abbreviations for 8-hydroxyquinoline, 5-iodouracil and 5-nitrouracil are 8HQ, 5Iu and 5Nu, respectively, [b]Compounds 5Iu and 5Nu were shown to be inactive antimicrobials, [c]Minimum concentration that inhibits the growth of microorganisms

(8HQ-Hg-8HQ) (Anjaneyulu *et al*., 1982). It was suggested that when the high lipophilic metal complex (8HQ-Hg-8HQ) reached the site of action and was dissociated into 1:1 charged complex $(8HQ\text{-}Cu)^+$ and free ligand 8HQ (Anjaneyulu *et al*., 1982). Consequently, the formed charged complex will become the toxic entity by interacting and blocking the metal binding sites on enzymes that involves in the biosynthesis of pteridine (Anjaneyulu *et al*., 1982). By the same analogy, the dissociation of mixed ligand metal complexes (1-6) gave rise to (1:1) active $(8HQ\text{-}M)^+$ charged complex accounting for their antimicrobial activity, together with inactive free uracils (5Iu or 5Nu). Thus, the lower antimicrobial activity of complexes 1-6, as compared to the free ligand (8HQ), could be attributed to an antagonistic effect of the free ligand (uracils) and the so formed charged complex $(8HQ\text{-}M)^+$. As a result, the charged complex reduced its ability of N,O atoms electron doners to chelate metal ions that are essential for the metabolic processes when compared to the free N,O electron doners of 8HQ. Previously, 8HQ was reported to be good antimicrobials (Shen *et al*., 1999) against many strains of bacteria e.g. *Micrococcus flavus* ATCC 10240 (MIC 53.77 μM), *B. subtilis* ATCC 6633 and *B. cereus* ATCC 11778 (MIC 215.78 μM). Antifungal activity of 8HQ was observed against *C. albicans* ATCC 10231 (MIC 215.78 μM), *S. cerevisiae* ATCC 2366 (MIC 107.55 μM) and *Penicillium raistrikii* ATCC 10490 (MIC 53.77 μM). It also exhibited bactericidal activity with comparable potency against non-replicating and replicating *Mycobacterium tuberculosis* (Darby and Nathan, 2010) including antimalarial action (Shaw *et al*., 2010). Aqueous preparation (0.5%) of 8HQ displayed strong antigrowth activity against clinical isolates of *S. aureus*, MRSA and vancomycin-intermediate *S. aureus* with MIC of 86.18 μM (Short *et al*., 2006). Sulfate salt of 8HQ was reported to inhibit *in vitro* accumulation of cariogenic microorganisms as well as to be the most effective anticalculus and antiplaque agents (Depalma *et al*., 1976). In addition, 8HQ also showed selective inhibition against many human intestinal bacteria (Jeon *et al*., 2009). Moreover, the 8HQ was reported to exert anti-inflammatory activity through an inhibition of nitric oxide production (Darby and Nathan, 2010). Additionally, 8HQ-Cu-complex was used as a fungicide in agriculture and for the preservation of textiles, woods and paper (Kim *et al*., 2005).

It is notable that 8HQ and its metal complexes 1-6 showed inhibition against resistant pathogens including gram-positive and gram-negative bacteria e.g. *S. aureus* and *K. pneumoniae*, respectively.

CONCLUSION

In this study, 8HQ and mixed ligand metal complexes 1-6 were investigated for their antimicrobial effect. The complexes 1-6 displayed growth inhibition against many strains of both gram-positive and gram-negative bacteria with the MIC range of 575.71-718.76 μM. Whereas the free ligand, 8HQ was shown to be the very strong antimicrobial agent with the low MIC of 27.58 μM that was mostly observed for gram- positive bacteria which are resistant pathogens e.g. *S. aureus*, *E. faecalis* and diploid fungus, *C. albicans*. The findings reveal the versatility of the well known 8HQ as the very strong antimicrobial effects and as a potential ligand for the newly designed and synthesis of bioactive compounds. Herein, a series of 8HQ transition metal complexes as novel antimicrobials has been reported.

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